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Lymphocytic gastritis resembling graft-vs.-host disease following autologous hematopoietic cell transplantation

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ABSTRACT

Although cutaneous graft-vs.-host disease (GVHD) has been noted after autologous hematopoietic cell transplantation, intestinal involvement has not been well documented. We evaluated 197 patients undergoing autologous transplantation for intestinal symptoms; the source for hematopoietic cells was marrow (n=32), peripheral blood stem cells (n=146), or both (n=19). Patients with persistent nausea, vomiting, and anorexia after day 20 underwent upper intestinal endoscopy and mucosal biopsy. Eight patients (4.1%) had diffuse edema, erythema of gastric mucosa, and histological evidence of lymphocytic gastritis with focal apoptosis of crypt epithelial cells—typical of the findings in acute GVHD. All studies for viral, fungal, or bacterial causes were negative. Two patients showed evidence of GVHD in skin and liver, respectively. All patients received 1 mg/kg/day of oral prednisone for 10 days; symptomatic improvement often occurred within days of therapy onset. At the end of corticosteroid treatment, complete resolution of symptoms was seen in all eight patients. In one patient, elevated serum alkaline phosphatase levels gradually normalized over the ensuing 3–4 weeks. When followed up 3 months after treatment, all patients remained symptom-free without evidence of recurrent intestinal symptoms. We concluded that recipients of autologous hematopoietic cells may develop intestinal symptoms caused by a lymphocytic gastritis that is typical of acute GVHD. Patients with this syndrome promptly responded to treatment of a short course of prednisone. The pathogenesis of gastric epithelial damage after autologous transplant is unknown.

KEY WORDS

Gastritis • Marrow transplantation • Stem cell transplantation • Cytoreductive therapy

INTRODUCTION

Acute graft-vs.-host disease (GVHD), a frequent complication of allogeneic marrow transplantation, is clinically characterized by skin, intestinal, and hepatic damage [1,2]. A cutaneous GVHD-like syndrome has also been described following nonallogeneic marrow transplantation, affecting seven of 96 autologous and two of 19 syngeneic marrow recipients in two recent series [3,4]. This autologous GVHD clinically and histologically resembles GVHD after allogeneic transplantation, but generally involves only the skin. Although intestinal and hepatic involvement are not prominent features of autologous GVHD [3–6], diarrhea and mild liver function abnormalities have been described in a small number of patients [7,8]. The development of GVHD after autologous transplantation is thought to result from a lack of regulation of the immune response by a reconstituting immune system [9].

We report here a study of eight patients who had enigmatic nausea, vomiting, and anorexia following autologous marrow or peripheral blood stem cell (PBSC) transplants. Each patient had a lymphocytic gastritis histologically indistinguishable from acute GVHD and each responded to therapy with corticosteroids.

MATERIALS AND METHODS

Patient selection

From May 1993 through February 1995, 197 patients underwent high-dose cytoreductive therapy followed by

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infusion of autologous marrow (n=32), stem cells (n=146), or both (n=19) at the Fred Hutchinson Cancer Research Center [10,11]. Underlying diagnoses included non-Hodgkin's lymphoma (53), breast cancer (50), Hodgkin's lymphoma (16), acute myelogenous leukemia (19), multiple myeloma (16), ovarian cancer (6), Ewing's sarcoma (6), acute lymphocytic leukemia (4), and other solid tumors (27). Conditioning regimens included 12 mg/kg of busulfan (BU), 100 mg/M^2 of melphalan, and 350–550 mg/M^2 of thiotepa (n=61); 100 mg/kg of cyclophosphamide, 60 mg/kg of etoposide, and 12 Gy of total-body irradiation (TBI) (n=55); 12–20 mg/kg of BU and 120–200 mg/kg of cyclophosphamide (n=30); 14 mg/kg of BU, 120 mg/kg of cyclophosphamide, and 9–10.5 Gy of total-marrow irradiation (n=16); 8 mg/kg of BU, 60 mg/kg of cyclophosphamide, and 12 Gy of TBI (n=15); 14 mg/kg of BU and 400–600 mg/M^2 of thiotepa (n=11); 1 mg/M^2 of etoposide, 900 mg/M^2 of thiotepa, and 6 Gy of TBI (n=4); 12 Gy of total-marrow irradiation (n=4, all receiving second transplants); and 30 mg/kg of etoposide and 12 Gy of TBI (n=1). For patients receiving PBSC infusions, the mobilization regimens included granulocyte colony-stimulating factor (G-CSF) at 10–32 μg/kg alone (n=57) or after chemotherapy with 4 g/M^2 of cyclophosphamide (n=13); 4 g/M^2 of cyclophosphamide and etoposide 600 mg/M^2 (n=36); 3–4 g/M^2 of cyclophosphamide, 400–600 mg/M^2 of etoposide, and 105 mg/M^2 of cisplatin (n=28); 4 g/M^2 of cyclophosphamide and 175 mg/M^2 of taxol (n=19); and other regimens (n=12). More detailed methods and results of these mobilization schedules have been published [10,11]. The date of first infusion of PBSCs or marrow was termed "day 0," from which all subsequent events were dated. Post-transplant patients were followed on a daily basis until they engrafted and were medically stable, and then were returned to the care of the referring oncologist.

Evaluation of gastrointestinal symptoms

All patients who developed persistent gastrointestinal complaints after transplant were evaluated by the Gastroenterology/Hepatology Section at the Fred Hutchinson Cancer Research Center. Evaluation consisted of patient histories (particularly as related to current medications and risk factors for herpesvirus infection), physical examination, laboratory tests for liver and pancreatic disease, and imaging tests (ultrasound, computed tomography [CT] X ray) if indicated [2]. Esophagogastroduodenoscopy (EGD) was performed on all patients who had persistent nausea, vomiting, anorexia, abdominal pain, gastrointestinal bleeding, or difficulty swallowing. Our endoscopic protocol for transplant patients has been described [12,13]. Biopsy specimens were routinely taken from four sites in the gastric antrum plus any other mucosal area that appeared abnormal. Biopsy specimens were placed in B5 fixative for histology (hematoxylin-eosin, methenamine silver, and Brown-Hopps tissue Gram stains); in urea-containing medium for detection of *Helicobacter pylori* (CLO test, Delta West, Bentley, W. Australia); and in veal infusion broth for viral culture. Viral culture methods included both conventional fibroblast cell culture for microscopic examination of cytopathic alterations and centrifugation cell culture for rapid diagnosis of cytomegalovirus by indirect immunofluorescence [14].

Diagnosis of GVHD

Diagnosis of acute intestinal GVHD required all of the following elements: upper intestinal endoscopy showing abnormal mucosa in the stomach or duodenum [12,15,16]; histological findings in biopsy specimens of the gastric mucosa, showing apoptotic crypt epithelial cells and crypt cell dropout with or without focal lymphocytic infiltrates [16–20]; and negative results from viral cultures of gastric biopsy specimens, histologic stains of gastric biopsy specimens for bacteria and fungi (i.e., methenamine silver and Brown-Hopps tissue Gram stains), histological evaluation for viral cytopathic effect; and the CLO test for *Helicobacter pylori* (Delta West) [13,14].

RESULTS

Patients evaluated

We evaluated 31 patients who had persistent gastrointestinal symptoms after transplant. Sixteen of these patients underwent intestinal endoscopy with mucosal biopsy, including 14 who had upper endoscopic examinations and 2 who had both upper endoscopic and colonoscopic.

Patients with lymphocytic gastritis resembling GVHD

Characteristics. Eight patients with biopsy-proven lymphocytic gastritis resembling GVHD who had no evidence of gastrointestinal infection were identified from among 197 patients who had received autologous transplants, an incidence of 4.1% (Table 1). Seven had received autologous PBSC transplants for non-Hodgkin's lymphoma (n=2), breast cancer (n=4), and ovarian cancer (n=1); regimens for PBSC harvest are shown in Table 1. One patient with lymphoma had received autologous marrow. Seven had been conditioned with 12 mg/kg of BU, 100 mg/M^2 of melphalan, and 500 mg/M^2 of thiotepa; and one with 14 mg/kg of BU and 550 mg/M^2 of thiotepa. Dominant symptoms were nausea, vomiting, and anorexia leading to significant weight loss and a decreased sense of well-being. Diarrhea (more than three loose stools a day) and abdominal pain were seen in five and three patients, respectively. The diarrhea was not severe in any patient, but was characterized by intermittent watery stools accompanied by crampy abdominal pain. One patient (unique patient number [UPN] 8803) also had dysphagia. In seven of eight patients, the onset of intestinal symptoms occurred between day 20 and 50. One patient (UPN 8097) had continuous, unabated nausea, gagging, and retching that dated from the conditioning chemotherapy, and was followed by the development of vomiting at day 23. Onset of these symptoms occurred on day 0 (Table 1). Two weeks posttransplant, another patient (UPN 7844) had a skin rash and a skin biopsy specimen consistent with GVHD. Cutaneous manifestations of GVHD were absent in the other six patients. Concomitant with her gastrointestinal symptoms, another patient (UPN 8499) showed a 5- to 6-fold elevation of serum alkaline phosphatase, which was consistent with hepatic GVHD; serum aminotransferase enzymes, bilirubin, abdominal ultrasound, and CT were normal.

Endoscopic and histological findings. Endoscopic abnormalities included diffuse edema and patchy erythema in the prepyloric gastric antrum. Frank erosions or ulcerations were not present. In one patient (UPN 8855), these gross changes extended into the gastric body and fundus. Mucosal

Table 1. *Clinical features of 8 patients with lymphocytic gastritis resembling graft-vs.-host disease*

UPN[a]	Age	Sex	Diagnosis	PBSC mobilization[b] and pretransplant conditioning regimens[c]	Type of transplant[d]	Gastrointestinal symptoms				
						Day of onset/ day of endoscopy	Nausea or vomiting	Anorexia	Diarrhea	Pain
7844	40	M	Lymphoma	N/A	Autologous marrow	35/43	Y	Y	Y	Y
7853	58	F	Lymphoma	BU, Mel, TT CY, etoposide, G-CSF	Autologous PBSC	30/239	Y	Y	N	N
8097	64	F	Breast cancer	BU, Mel, TT CY, taxol, G-CSF	Autologous PBSC	0/33	Y	Y	Y	N
8499	50	F	Breast cancer	BU, TT G-CSF	Autologous PBSC	30/50	Y	Y	N	N
8639	57	F	Breast cancer	BU, Mel, TT G-CSF	Autologous PBSC	50/69	Y	Y	Y	Y
8803	53	F	Ovarian cancer	BU, Mel, TT CY, taxol, G-CSF	Autologous PBSC	40/69	Y	Y	N	N
8855	50	F	Lymphoma	BU, Mel, TT CY, G-CSF	Autologous PBSC	25/33	Y	Y	Y	Y
9002	65	F	Breast cancer	BU, Mel, TT CY, etoposide, cisplatin BU, Mel, TT	Autologous PBSC	23/44	Y	Y	Y	N

[a] *Unique patient number.*
[b] *Cyclophosphamide (CY), 3–4 g/M²; etoposide, 400–600 mg/M²; cisplatin, 105 mg/M²; taxol, 175 μg/M²; granulocyte colony-stimulating factor [G-CSF], 10–16 μg/kg.*
[c] *BU, Mel, TT; 12 mg/kg of busulfan, 100 mg/M² of melphalan, and 500 mg/M² of thiotepa: BU, TT; 14 mg/kg of busulfan and 500 mg/M² thiotepa.*
[d] *PBSC, peripheral blood stem cells.*

biopsy from the gastric antrum revealed a picture of lymphocytic gastritis consistent with acute GVHD (Fig. 1A) [16–20]. Individual epithelial cell necrosis (apoptosis) was seen at the base and sides of crypts (Fig. 1B). Infiltration of lamina propria and crypt epithelium by lymphocytes was present to a variable extent. None of the patients had evidence of infection with viruses, bacteria, or fungi, and no viral cytopathic effect was seen histologically.

Response to therapy. Before endoscopic diagnosis and without success, patients had been treated empirically with antacids, H2 receptor antagonists, sucralfate, omeprazole, and various antiemetics including antihistamines, benzodiazepines, and serotonin antagonists. Three patients had been treated with a prokinetic agent (cisapride) and two patients had been prescribed amoxicillin, metronidazole, omeprazole for a presumed but unproven *Helicobacter pylori* infection. Following histological diagnosis of lymphocytic gastritis, all patients received 1 mg/kg/day of oral prednisone for 10 days, then 0.5 mg/kg/day for 3 days, then 0.25 mg/kg/day for 3 days, and then the prednisone was discontinued. Symptomatic improvement often occurred within days of therapy onset. At the end of steroid treatment, complete resolution of symptoms was seen in all eight patients. In one patient (UPN 8499) who also had simultaneous serum alkaline phosphatase elevation, the alkaline phosphatase level gradually normalized over the ensuing 3–4 weeks. When followed up at 3 months after treatment, all remained symptom-free without evidence of recurrence. Endoscopy was not repeated in any patient.

Diagnoses in 23 patients not classified as having lymphocytic gastritis

Among 23 other patients who were evaluated for persistent gastrointestinal symptoms, there were nine whose symptoms were attributed to regimen-related toxicity involving the intestinal mucosa or liver; five whose symptoms were caused by infection (cholecystitis [2], typhlitis caused by a clostridial organism [1], phlegmonous gastritis [1], and enterococcal sepsis [1]); one each with eosinophilic gastritis (probably drug-related), gastric antral vascular ectasia, and recurrent malignancy; and six with unexplained symptoms. This latter group is interesting because they probably also had lymphocytic gastritis that resembled GVHD, but there was a reluctance on the part of pathologists and treating physicians to make an unequivocal diagnosis of this disease; their symptoms persisted for many weeks until death (four patients) or treatment with prednisone for another indication (two patients).

DISCUSSION

Eight patients developed persistent unexplained nausea, vomiting, and anorexia following autologous transplant with marrow or PBSCs. We believe that these gastrointestinal symptoms were because of a lymphocytic gastritis indistinguishable from acute GVHD for several reasons: 1) these symptoms are typical of acute GVHD in allogeneic marrow recipients [12,15,16,21]; 2) empiric antiemetic therapies failed to have an impact on the symptoms; 3) no infections could be identified; 4) both the endoscopic and histologic appearance of the gastric mucosa were characteristic of acute GVHD [16–20]; and 5) treatment with a short course of prednisone resulted in cessation of symptoms.

While it is common for patients to have nausea, vomiting, anorexia, and diarrhea during and after high-dose cytoreductive therapy, these symptoms and the histologic abnormalities in the intestinal mucosa caused by such thera-

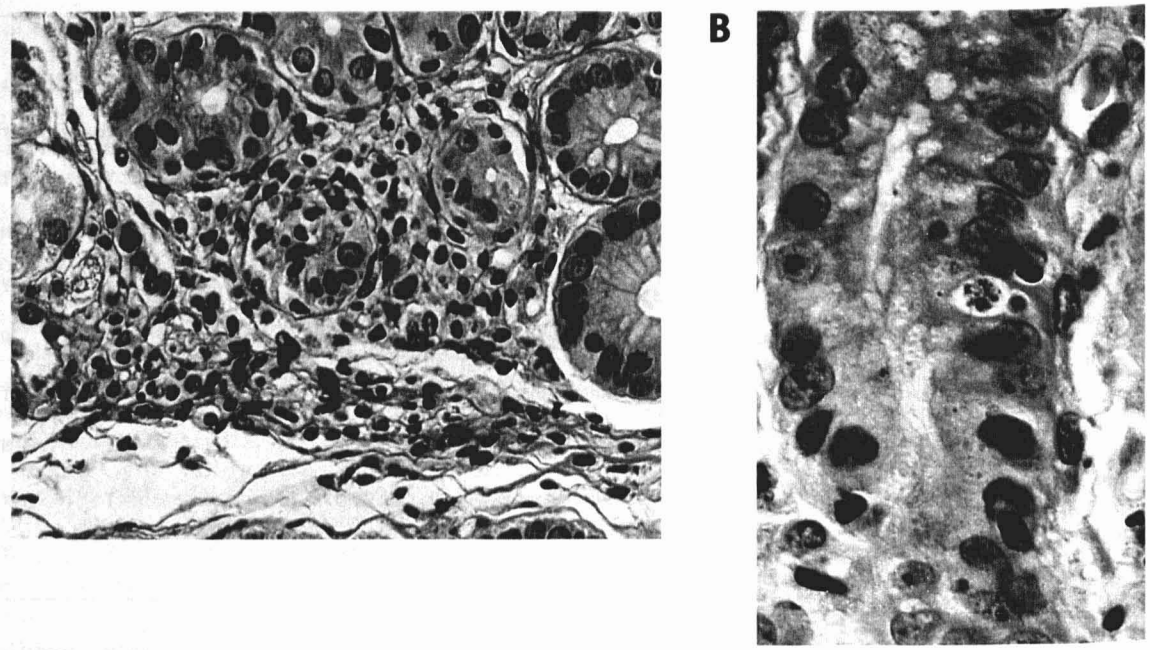

Figure 1. Photomicrographs of gastric biopsy specimens, demonstrating alterations characteristic of acute graft-vs.-host disease
A *(UPN 8855, H&E ×500), lymphocytic infiltration of the lamina propria and mucosal crypts. Note the drop-out of epithelial cells in involved crypts.* **B** *(UPN 7853, H&E ×800), focal epithelial cell apoptosis is seen at the base of a gastric crypt.*

py usually resolve by day 20 posttransplant [22,23]. Some regimens, however, can produce mucosal damage that is more severe and prolonged than is normal [10,24]. For allogeneic marrow recipients, the mean day of onset of acute GVHD is day 19 [25]. The presence of persistent nausea, vomiting, and anorexia after day 20 in an allogeneic marrow recipient points to either acute GVHD of the upper gut, herpesvirus infection, or medication-induced nausea [12,15,16,21]. Gastric GVHD is by far the most common cause for enigmatic nausea and vomiting in allogeneic marrow transplant patients who are beyond day 20, accounting for 81–86% of cases in a recent prospective study [21]. Herpes simplex virus and cytomegalovirus are now unusual causes of these symptoms because of the use of prophylactic antiviral agents [26]. Nonetheless, we looked for these viruses in the autologous graft recipients reported here and found none. This is important because apoptotic cells, the histologic hallmark of immune-mediated epithelial cell injury, can be seen occasionally in the intestinal epithelium infected by cytomegalovirus [14,27].

A syndrome resembling mild GVHD has been reported in approximately 8% of patients receiving autologous or syngeneic bone marrow transplantation [4]. In these patients, a maculopapular rash, clinically and histologically indistinguishable from allogeneic GVHD, appears usually between the first and third week after transplant. More recently, GVHD was induced deliberately by treating patients with cyclosporine following autologous marrow infusion to explore the potential therapeutic efficacy of a graft-vs.-tumor effect [6,7,28]. In these patients, a mild form of GVHD that was confined to the skin resolved spontaneously or after a short course of corticosteroid treatment. In a small series that reported on 4 patients with GVHD after syngeneic bone marrow transplantation [8], one had concomitant diarrhea and three had elevated serum aminotransferase enzymes and bilirubin. Intestinal and hepatic involvement by GVHD was suggested by the authors, but no histological confirmation was obtained. Our cases demonstrate that gastric epithelium is a target for autologous GVHD. The upper gastrointestinal findings were isolated events in six of eight patients who had neither previous nor ongoing skin or liver manifestations of GVHD.

In human and rodent studies, induction of autologous GVHD is associated with the emergence of cytotoxic T cells that recognize class II human leukocyte antigens (HLAs) [9,29]. Ablation of a T cell–dependent regulatory mechanism in the peripheral lymphoid compartment by high-dose chemotherapy or TBI allows further expansion of these autoreactive T cells [30–32]. A clear explanation for the predominance of skin involvement is lacking. As shown in this study, symptomatic and histologic involvement of the stomach by a GVHD-like gastritis appears to be rare; it was observed in <5% (8 of 197) of our cohort. Endoscopy was performed in only those who remained symptomatic, thus the exact incidence cannot be determined because some patients may be minimally symptomatic despite histological involvement. Indeed early in our experience, there was some reluctance on the part of treating physicians to accept this diagnosis or to consider endoscopic biopsy in recipients of autologous hemotopoietic cells. In our series, symptomatic gastritis was seen as frequently in patients who received PBSCs (7 of 146) as in those who received autologous marrow infusion (1 of 32; $p > 0.9$). These eight patients are not different from those who did not develop this syndrome with regard to type of cancer, conditioning regimen, PBSC harvest protocol, days between PBSC harvest and reinfusion, or concomitant use of growth factors (data not shown).

Even though a large number of autologous marrow transplants have been carried out at our center over the last two decades, we had not recognized this syndrome. It is possible that recently introduced methods of autologous transplantation may be responsible; for example, new conditioning regimens, PBSC harvest regimens, and different lymphocyte profiles after the infusion of autologous PBSCs vs. marrow progenitor cells. Melphalan and thiotepa may cause substantial gastrointestinal mucosal toxicity [10,11], and the use of these agents in combination with BU may play an etiologic role in this syndrome by altering epithelial cells and creating targets for subsequent T lymphocyte–mediated apoptosis. Although there was no apparent difference in the incidence of this syndrome between recipients of PBSCs vs. marrow, the number of patients receiving marrow was comparatively small. Seven of our eight patients had received PBSCs but one recipient of autologous marrow did have lymphocytic gastritis consistent with GVHD.

GVHD does not usually enter the differential diagnosis of anorexia, nausea, and vomiting following autologous transplant because of a common belief that visceral GVHD does not occur after autologous transplantation. This belief appears untrue. Physicians caring for patients after autologous transplant should be aware of gastric GVHD as a potential cause for persistent intestinal symptoms.

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